CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20759/20760

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**(i) 20-759** **(ii) 20-760**
Submission Date:	December 27, 1996
Drug Products & Dosage Forms	**(i)** Trovafloxacin Mesylate (CP-99,219) Tablets TROVAN® 100 and 200 mg Oral Tablets **(ii)** Alatrofloxacin Mesylate (CP-116,517) Injection TROVAN® 100, 200, and 300 mg IV Solution
Sponsor:	Pfizer Central Research Groton, CT
Type of Submission:	NME
Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In Date:	January 7, 1997

I. BACKGROUND

Trovafloxacin and alatrofloxacin are synthetic fluoronaphthyridone antibiotics which are similar in structure and mechanism of action to the fluoroquinolone class of antibiotics. Trovafloxacin is being developed as an immediate release oral film coated tablet and alatrofloxacin as the intravenous (iv) solution. Alatrofloxacin is the bis-alanyl iv form of trovafloxacin and was formulated as such because of solubility problems with trovafloxacin. Alatrofloxacin is by circulating to trovafloxacin *in vivo* following iv infusion. Both products will be marketed in the United States under the tradename TROVAN® and will be available as 100 and 200 mg tablets and 100, 200, and 300 mg solution for iv infusion following dilution. In addition to the U.S., the sponsor also plans to market both formulations in Europe, Canada, and several other countries throughout the world in 1997.

II. INDICATIONS and DOSAGES

TROVAN® is being developed for the treatment of a variety of infectious diseases caused by several classes of bacterial pathogens, including certain drug-resistant strains (e.g., *Strep. pnuemoniae, Staph. aureus*). The proposed oral doses are 100 to 200 mg given once per day and the iv doses range from 200 to 300 mg per day in adults 18 years of age and older.

The proposed indications and dosages are listed below. Since several of the indications were studied using TROVAN® iv followed by the tablets, it was agreed upon by the Agency that the sponsor could combine the two NDA' s into one integrated submission and that the Agency would review them simultaneously.

DOSAGE GUIDELINES		
INFECTION*/LOCATION AND TYPE	DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION	TOTAL DURATION
Nosocomial Pneumonia	300 mg I.V. followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections, Complicated, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis - Elective Colorectal Surgery	200 mg I.V. or oral	Single dose
Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy	200 mg I.V. or oral	Single dose
Skin and Skin Structure Infections, Uncomplicated	100 mg Oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections (cystitis)	100 mg oral	3 days
Bacterial Prostatitis	200 mg oral	28 days
Acute, Uncomplicated Gonorrhea	100 mg oral	Single Dose
Non-Gonococcal Urethritis/ and Cervicitis	200 mg oral	5 days
Pelvic Inflammatory Disease	200 mg oral or 200 mg I.V. followed by 200 mg oral	14 days

* due to the designated pathogens

III. HUMAN PK/BIOAVAILABILITY SYNOPSIS

Item 6: Human Pharmacokinetics and Bioavailability was comprised of 50 volumes containing data from 46 Phase I PK studies of trovafloxacin tablets and alatrofloxacin iv infusion. Of these 46 total studies, data from at least 32 studies were incorporated into the proposed labeling, and thus, the majority of these 32 studies were reviewed. All sections of the submission, except for the CMC section (Items 3 and 4), were provided by the sponsor as an electronic submission and was accessed from the reviewers' personal computers. This includes the entire contents of Item 6 and the raw serum drug

concentration-time and PK data for selected studies from Item 6 which were requested by the reviewer to be provided by the sponsor. Item 6 was also provided for review as a paper copy.

A synopsis of the basic pharmacokinetic characteristics of both compounds is as follows:
Tablet Absorption: Tmax was 1-2 hrs; absolute bioavailability of trovafloxacin 100 mg tablets was 88%; oral availability not effected by food (high-fat breakfast) at 200 mg dose.
Alatrofloxacin Hydrolysis: hydrolyzed by plasma esterases; plasma alatrofloxacin concentrations are non-quantifiable within 5-10 minutes after the end of a 60 minute infusion.

Distribution: trovafloxacin volume of distribution (Vd_{ss}) after iv alatrofloxacin was serum protein binding was moderate ; distributes well into tissues/fluids, including lung, gynecologic, prostate tissues, blister fluid.

Metabolism: Phase II conjugation, i.e., glucuronidation (major), sulfation (minor), N-acetylation (major); minimal oxidative metabolism; N-acetyl trovafloxacin has some microbiological activity.

Excretion/Elimination: total recovery of trovafloxacin was 86% (63% from feces, 23% from urine); excretion of unmetabolized trovafloxacin was primarily via feces (~40%) and/or bile; minor renal elimination (<10%); elimination T½ 10-12 hrs.

Single Dose PK - Trovafloxacin: dose proportional PK from 30 to 1000 mg (solution or oral suspension), and from 100 to 200 mg (tablets)
Single Dose PK - Alatrofloxacin IV: dose proportional PK from 100 to 300 mg

Multiple Dose/Steady-State PK: linear and stationary PK; C_{ss} attained by 3rd daily dose; $Cmin_{ss}$ 0.4-0.6 ug/mL.

	$Cmax_{ss}$ (ug/mL)	AUC_{ss} (ug.hr/mL)
100 mg PO	~1.5	~12
200 mg PO	~3.0	~30
200 mg IV	~3.0	~30
300 mg IV	~4.0	~45

Special Populations:

Hepatic Impairment (mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) chronic cirrhosis) - systemic exposure (i.e., AUC) increased and T½ prolonged after repeated 100 mg (mild) and 200 mg (moderate) doses vs matched controls.

Renal Impairment, including dialysis - no significant effect on trovafloxacin PK; dialysis did not appreciably remove trovafloxacin from serum.

Age - no significant effect on trovafloxacin PK.

Gender - females show increases in systemic exposure (i.e., AUC) of ~16% and Cmax of ~40% after repeated 200 mg doses; the increases can be attributed to the lower body weights of females.

Drug Interactions:

No significant effect of trovafloxacin on the PK of caffeine, digoxin, warfarin (including PT, INR, and APTT as pharmacodynamic measures), cyclosporine, and theophylline all at steady-state.

No significant effect of omeprazole, calcium carbonate (TUMS®), or cimetidine on trovafloxacin PK.

Significant reduction in oral availability of trovafloxacin by Maalox TC (i.e., Al/Mg antacid), sucralfate, and ferrous sulfate, presumably mainly through complexation with trovafloxacin. Morphine iv also significantly reduces trovafloxacin oral availability, presumably through opiate-induced reduction in gastric motility and/or gastric emptying.

There were no population pharmacokinetics analyses or pharmacodynamic analyses (i.e., relation (and/or correlation) of trovafloxacin levels in tissues/fluids of infection or other PK parameters with the MIC_{90} of the associated pathogens) included in the submission.

The bioequivalence between the proposed commercial formulation for the trovafloxacin mesylate tablet (100 mg) and the Phase III clinical trials tablet (100 mg) was demonstrated. There was no need to establish bioequivalence between the proposed commercial formulation for the 200 mg tablet and the Phase III 100 mg clinical trials tablet since both 100 mg and 200 mg tablet strengths were manufactured from a

IV. RECOMMENDATION

The information for Item 6: Human Pharmacokinetics and Bioavailability of NDA 20-759 / 20-760 for trovafloxacin mesylate tablets / alatrofloxacin mesylate intravenous solution has been reviewed and was found to be acceptable and adequate to support approval of both oral and iv formulations.

V. COMMENTS FOR THE SPOSNOR

1. Study 154-024 (PET study) - the study report was classified as "interim" by the sponsor, i.e., with respect to the data for the 19 subjects enrolled at this clinical site (study dates 11/95-5/6/96). However, the interpretation of this is not clear, i.e., whether there will be more data generated from this site, or whether the data already generated and reported is in final form. Another concern is that no information regarding the formulation/manufacture, purity, etc. of the iv trovafloxacin was provided with the study report. It is recommended that the sponsor provide further clarification of the term "interim" for this study report, and also provide additional formulation information for trovafloxacin iv. The Agency will provide a full review of this study following submission of the final study report by the sponsor.

At such time, the Agency . the dissolution method and specification for trovafloxacin mesylate tablets.

/S/

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

/S/

RD/FT signed by Funmi Ajayi, Ph.D (Acting TL) _____
Briefing (12/8/97) Attendees: F. Ajayi, J. Lazor, P. Marroum, J. Collins, J. Hunt, J. Jenkins, B. Leissa

cc:
Div. File: NDA 20-759; 20-760
HFD-590 (B. Leissa, TL/MO; P. Coyne, MO)
HFD-590 (P. Fogarty, PM/CSO)
//
//
HFD-340 (Viswanathan)
HFD-205 (FOI)
HFD-880 (Division File)
HFD-880 (F. Ajayi; P. Colangelo)
CDR (Barbara Murphy)